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ART UNIT	**PAPER NUMBER**
1818	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/776,190	H.P. Josel et al.
Examiner	**Group Art Unit**
Neal A. Musto, Ph.D.	1818

☒ Responsive to communication(s) filed on *5 Sep 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-30* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The amendment filed 5 Sept 1997 has been received and entered. Claims 1-30 are pending.

Claims 1-30 are currently under consideration.

2. The amendments to claims 8, 12 and 21 were not entered due to the inconsistency between the claim language and the amendment, for example, in claim 8 the phrase *"one of the claims 1-5"* was requested to be deleted, however no such language is found in the claim. The applicant should amend so as to clarify the issue. In an effort to render compact prosecution, it is recognized that the intention was to make these claims dependent upon claim 7 and as such these claims were analyzed as being so dependent.

3. Rejections made in paper number 4, but not repeated herein are withdrawn in view of applicant's arguments filed 5 Sept 1997.

Claim Rejections - 35 USC § 112

Claims 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27-30 provides for the use of conjugates of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is

intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3, 5, 6, 7, 9, 11, 12, 13, 15, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dattagupta *et al* **[Dattagupta *et al.* 1988]**.

Dattagupta *et al* disclose a conjugate comprising a polymeric carrier conjugated with multiple fluorescein molecules (*i.e.*, both a marker and a hapten), wherein the monomeric units are nucleotides and a marker (*viz.*, IgG or Protein A) is specifically linked to the 3' end (see example 1). Moreover, the reference discloses the use of psorlen derivatives to photochemically label the DNA with either fluorescein, rhodamine or biotin, and psorlen is known to specifically react with pyrimidines thereby specifically labeling those positions wherein a pyrimidine is located. Further, the carrier comprises a double stranded nucleic acid of 72 to 1353 monomeric units. This reads on the instant claims 1, 3, 5, 6, 7, 9, 11, 12, 13, 15, 16 and 17, which are drawn to conjugates comprising a polymeric carrier, 1-10 hapten molecules and 1-10 marker or solid phase binding groups, and the monomeric units are nucleic acids of 3-80 monomeric units.

6. Claims 1-6, 11, 12, 15, 16, 27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Bredehorst *et al* **[Bredehorst *et al.* 1991]**.

Bredehorst *et al* disclose a conjugate comprising a polymer of 21 amino acids (*viz.*, insulin) which contains 3 hapten (*viz.*, fluorescein) and one solid-phase binding group (*viz.*, DNP/ anti-DNP). This conjugate is used in a competitive immunoassay. This reads on the instant claims 1-6, 11, 12, 15, 16, 27, 29 and 30 directed to conjugates comprising a polymeric carrier 1-10 hapten molecules and 1-10 marker or solid phase binding groups, and the monomeric units are amino acids used in a competitive immunoassay.

7. Claims 21, 23, 24, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al* **[Smith *et al.* 1989]**.

Smith *et al* discloses the solid phase synthesis of oligonucleotides containing at predetermined positions monomers capable of further derivatization (i.e. with fluorescein, a hapten, binding group and marker group) through amino functional groups. These functional groups are taught to be protected by a wide variety of protecting groups (see col 10, line 66+ and col 11, line 1+), which are removable under selective conditions (*e.g.*, example 11), including acidic or basic conditions. This synthesis of hapten substituted oligonucleotide can be accomplished either co-synthetically (example 11) or post-synthetically (examples 12, 13, 14). This reads on the instant claims 21, 23, 24, 25 and 26 drawn to a process for producing a conjugate comprising a polymeric carrier which contains one hapten molecule and one marker group coupled to reactive side groups (amino) wherein the monomeric units are nucleotide

analogues. Further limitations include addition either post or co synthetically and the use of selectively cleaveable protective groups (i.e. acid stable or labile).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 8, 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta *et al* **[Dattagupta *et al.* 1988]**, in view of Bredehorst *et al* **[Bredehorst *et al.* 1991]**, and further in view of Nielsen *et al* **[Nielsen *et al.* 1996]** for reasons made of record in paper number 4 in the rejection of the original claims 8, 10.

10. Claims 2 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* **[Bredehorst *et al.* 1991]**, in view of Gadow *et al* **[Gadow *et al.* 1987]** for reasons made of record in paper number 4 in the rejection of the original claim 14.

11. Claims 21, 23, 24, are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* **[Smith *et al.* 1989]** for reasons made of record in paper number 4 in the rejection of the original claims 21, 23, 24.

12. Claims 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredhorst *et al* **[Bredehorst *et al.* 1991]** in view of Smith *et al* **[Smith *et al.* 1989]** for reasons made of record in paper number 4 in the rejection of the original claims 27-30.

13. Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst *et al* **[Bredehorst *et al.* 1991]**, in view of Berzofsky *et al* **[Berzofsky *et al.* 1989]** for reasons made of record in paper number 4 in the rejection of the original claims 18-20.

14. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al* **[Smith *et al.* 1989]**, in view of Buchardt *et al* **[Buchardt *et al.* 1992]**.

Smith *et al* teaches the solid phase synthesis of oligonucleotides containing at predetermined positions monomers capable of further derivatization (i.e. with fluorescein, a hapten, binding group and marker group) through amino functional groups. These functional groups are taught to be protected by a wide variety of protecting groups (see col 10, line 66+ and col 11, line 1+), which are removable under selective conditions (*e.g.*, example 11), including acidic or basic conditions. This synthesis of hapten substituted oligonucleotide can be accomplished either co-synthetically (example 11) or post-synthetically (examples 12, 13, 14). They do not teach oligomeric carrier as being synthesized from amino acid derivatives.

However, Buchardt *et al* teach the production of oligomeric compounds comprising a hybrid (i.e., derivative) between nucleotide bases and amino acid, called peptide nucleic acids (PNA). These structures have a peptide chain backbone with nucleobases and amino acids side

chains, both of which have available amino reactive functionalities (see fig 8). These oligomers are polymerized with solid support chemistry characteristic of peptide chemical synthesis. Thus, it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to utilize PNA as a carrier molecule because the unique properties found in this class of molecule (i.e., stability). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to do so since it would allow greater flexibility and choice of the carrier.

Response to Arguments

15. Applicant's arguments with respect to claims 1, 3, 5-7, 9, 11-13 and 15-17 have been considered but are moot in view of the new ground(s) of rejection.

16. Applicant's arguments with respect to claims 2-6, 11, 12 and 16 have been considered but are moot in view of the new ground(s) of rejection.

17. The prior rejection of claims 8 and 10 under 35 U.S.C. § 103 as being unpatentable over Dattagupta *et al* **[Dattagupta *et al.* 1988]**, in view of Bredehorst *et al* **[Bredehorst *et al.* 1991]**, and further in view of Nielsen *et al* **[Nielsen *et al.* 1996]** as set forth in the last Office Action mailed 5 May 1997 is maintained.

Applicant's arguments have been fully considered but they are not persuasive. Applicant present arguments that the primary reference (Bredehorst *et al)* does not teach the limitations of

the present claims and that the secondary reference (Nielsen *et al*) merely teaches the synthesis of peptide nucleic acids, thus the rejection is not valid.

In response to Applicant's argument that the rejection is not valid because the teachings of the combined references do not render the invention obvious, it should be noted that Bredehorst *et al*, in fact, does disclose the limitations of the present claims by teaching the use of a peptide carrier molecule which comprises a peptide to which haptens (DNP) and marker (fluorescein) have been covalently linked at specific sites. It does not teach the use of peptide nucleic acids as the oligomeric backbone. Peptide nucleic acids as polymeric units is taught by the secondary reference, Nielsen *et al*, which discloses the synthesis of this class of oligomeric compounds.

For the reasons set forth above and for the reasons set forth in the last Office Action the rejection of the claimed invention is maintained.

18. The prior rejection of claim 14 under 35 U.S.C. § 103 as being unpatentable over Bredehorst *et al* **[Bredehorst *et al.* 1991]**, in view of Gadow *et al* **[Gadow *et al.* 1987]** as set forth in the last Office Action mailed 5 May 1997 is maintained.

Applicant's arguments have been fully considered but they are not persuasive. Applicant present arguments that Gadow *et al* is merely cited as teaching the use of metal chelates as markers and Bredehorst *et al* does not disclose the limitations of the present claims.

In response to Applicant's argument that the rejection is no longer valid because Gadow *et al* is merely cited as teaching the use of metal chelates as markers and Bredehorst *et al* does

not disclose the limitations of the present claims, the cited reference teaches the use of a peptide carrier molecule which comprises a peptide to which haptens (DNP) and marker (fluorescein) have been covalently linked at specific sites. This meets the limitations disclosed in the independent claim 2, from which claim 14 depends. Thus, Bredehorst *et al*, in fact, does disclose the limitations of the present claims.

For the reasons set forth above and for the reasons set forth in the last Office Action the rejection of the claimed invention is maintained.

19. The prior rejection of claim 21, 23 and 24 under 35 U.S.C. § 103 as being unpatentable over Smith *et al* **[Smith *et al.* 1989]** as set forth in the last Office Action mailed 5 May 1997 is maintained.

Applicant's arguments have been fully considered but they are not persuasive. Applicant present arguments that the present invention is not obvious in view of Smith *et al* because there is not suggestion to utilize the simultaneous introduction of labeling groups and haptens.

In response to applicant's argument that there is no suggestion within the reference of the instant invention, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941

(Fed. Cir. 1992). In this case, the reference clearly teaches that one can positionally react fluorescein (both a marker and a hapten) an specific positions on the oligonucleotide, thus one skilled in the art would have recognized that the DNA could be modified in a manner disclosed in the instant claims.

For the reasons set forth above and for the reasons set forth in the last Office Action the rejection of the claimed invention is maintained.

20. The prior rejection of claims 27-30 under 35 U.S.C. § 103 as being unpatentable over Bredhorst *et al* **[Bredehorst *et al.* 1991]** in view of Smith *et al* **[Smith *et al.* 1989]** as set forth in the last Office Action mailed 5 May 1997 is maintained.

Applicant's arguments have been fully considered but they are not persuasive. Applicant present arguments that the rejection is no longer valid because Bredhorst *et al* does not show the limitations of the present invention and Smith *et al* do not overcome the failure of the primary reference to show the present invention.

In response to Applicant's argument that Bredhorst *et al* does not show the limitations of the present invention and Smith *et al* do not overcome the failure of the primary reference, the cited primary reference teaches the use of a peptide carrier molecule which comprises a peptide to which hapten (DNP) and marker (fluorescein) have been covalently linked at specific predetermined positions. This meets the limitations disclosed in the independent claim 1, from which claims 27-30 depend. Moreover, the primary reference also teaches the use of this

conjugate in an immunoassay for the hapten. Thus, Bredehorst *et al*, in fact, does disclose the limitations of the present claims.

For the reasons set forth above and for the reasons set forth in the last Office Action the rejection of the claimed invention is maintained.

21. The prior rejection of claim 18-20 under 35 U.S.C. § 103 as being unpatentable over Bredehorst *et al* **[Bredehorst *et al.* 1991]**, in view of Berzofsky *et al* **[Berzofsky *et al.* 1989]** as set forth in the last Office Action mailed 5 May 1997 is maintained.

Applicant's arguments have been fully considered but they are not persuasive. Applicant present arguments that the Berzofsky reference teach in a general way the interaction of antigens and antibodies and does not contain instruction for a person skilled in the art to arrive at conjugates with haptens and labeling groups at predetermined positions on the carrier and as such are an improper combination.

In response to applicant's argument that the combination of the references does not result in the present invention, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary reference, Bredhorst *et al*, teaches all the limitations of the claimed invention (see above) except the use of haptens comprising peptide epitope (claim

18), nucleic acids (claim 19) or peptidic nucleic acids (claim 20). The Berzofsky reference teaches that haptens may comprise single antigenic determinate that are small organic compounds including oligosaccharides (*i.e.*, DNA) or oligopeptides, thus suggesting the substitution of these hapten type for the hapten taught be the primary reference, Bredhorst *et al.*

For the reasons set forth above and for the reasons set forth in the last Office Action the rejection of the claimed invention is maintained.

Conclusion

22. No claims are allowed

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Neal A. Musto, Ph.D. whose telephone number is (703) 305-4505. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald E. Adams, Ph.D. can be reached at (703) 308-0570. The fax phone number for Group 1800 is (703) 305-7939 or (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

LORA M. GREEN
PRIMARY EXAMINER
GROUP 1800

Neal A. Musto, Ph.D.
FN08?761.FIN
December 5, 1997